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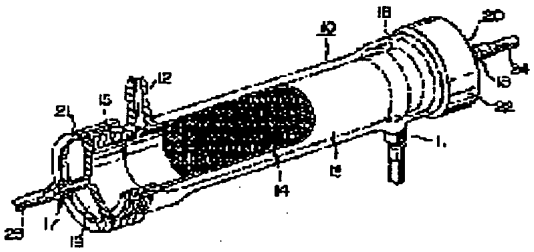
(54) HOLLOW FIBER MEMBRANE TYPE BODY FLUID PURIFICATION DEVICE AND ITS PRODUCTION

(57)Abstract:
PROBLEM TO BE SOLVED: To enhance safety and to lessen the elution of a hydrophilic polymer by constituting the device of hollow fiber membranes consisting of hydrophobic and hydrophilic polymers, an outside cylinder enclosing the hollow fiber membranes, sealing parts for sealing the hollow fiber membranes and the outside cylinder from each other and specifying the UV absorptivity of the hollow fiber membranes.
SOLUTION: If the main unit fluid purification device is a hemodialyzer, the hemodialyzer 10 is constituted by inserting a hollow fiber membrane bundle 14 consisting of the many hollow fiber membranes composed of the hydrophobic polymer and the hydrophilic polymer into the outside cylinder 13 having a dialyzate inflow inlet 11 and a flow passage outlet 12, then sealing both ends thereof with the sealing parts 15, 16 and liquid-tightly sealing both ends of the outside cylinder 13, respectively. Headers 19, 20 respectively having a body fluid flow passage inlet 17 and a body fluid flow passage outlet 18 are pressed to both ends of the outside cylinder 13. The assembled device is subjected to a leakage test after a treatment for hydrophilicity impartation and is sterilized by packing water of liquid having no injuriousness on the living body as a substituting liquid therein. The inclusion of the hydrophobic polymer and the hydrophilic polymer and the UV absorption below 0.05 are thus attained.



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* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] The hollow fiber which consists of a hydrophobic polymer and a hydrophilic polymer, and the outer case which surround this hollow fiber, the edge of this hollow fiber -- setting -- between this hollow fiber and these outer cases -- liquid -- with the closure section closed densely This hollow fiber, the body fluid passage containing the hollow fiber lumen ****(ed) by this closure section, the external surface of a hollow fiber, and the 2nd passage formed from this outer case, The body fluid passage inlet port and body fluid passage outlet which are connected with the exterior succeeding the lumen of this hollow fiber, The hollow fiber mold liquid purge which is a body fluid purge which has the 2nd passage inlet port and the 2nd passage outlet which were established in this outer case, and is characterized by UV (220nm) absorbance of the extract of the hollow fiber by dialysis mold hemodialysis apparatus Manufacturing License Standards being less than 0.05.
[Claim 2] The hollow fiber mold liquid purge according to claim 1 characterized by this hollow fiber containing fat soluble vitamin.
[Claim 3] Claim 1 to which this hydrophobic polymer is characterized by being polysulfone, polyether sulphone, and a polyamide thru/or a hollow fiber mold liquid purge given in 2.
[Claim 4] Claim 1 characterized by this hydrophilic polymer being a polyvinyl pyrrolidone or a polyethylene glycol thru/or a hollow fiber mold liquid purge given in 3.
[Claim 5] Claim 2 to which this fat soluble vitamin is characterized by being vitamin E thru/or a hollow fiber mold liquid purge given in 4.
[Claim 6] Claim 1 characterized by the average aperture of the detached core of this hollow fiber being 0.001-10 micrometers thru/or a hollow fiber mold liquid purge given in 5.
[Claim 7] The hollow fiber which consists of a hydrophobic polymer, a hydrophilic polymer, and fat soluble vitamin, the outer case which surround this hollow fiber, and the edge of this hollow fiber -- setting -- between this hollow fiber and these outer cases -- liquid -- with the closure section closed densely This hollow fiber, the body fluid passage containing the hollow fiber lumen ****(ed) by this closure section, the external surface of a hollow fiber, and the 2nd passage formed from this outer case, The body fluid passage inlet port and body fluid passage outlet which are connected with the exterior succeeding the lumen of this hollow fiber, The body fluid purge which has the 2nd passage inlet port and the 2nd passage outlet which were established in this outer case The manufacture approach of the hollow fiber mold liquid purge characterized by permuting this alcoholic water solution by the displacing solution which consists of a liquid which does not have harmfulness to water or a living body, and subsequently to this displacing solution sterilizing this hollow fiber in the condition of having been immersed after letting flow the alcoholic water solution of concentration with which this fat soluble vitamin is not eluted.
[Claim 8] The manufacture approach of the hollow fiber mold liquid purge according to claim 7 characterized by the alcoholic concentration of this alcoholic water solution being 1 - 70%.
[Claim 9] The manufacture approach of claim 7 to which this hydrophobic polymer is characterized by being polysulfone, polyether sulphone, and a polyamide thru/or a hollow fiber mold liquid purge given in 8.

[Claim 10] The manufacture approach of claim 7 characterized by this hydrophilic polymer being a polyvinyl pyrrolidone or a polyethylene glycol thru/or a hollow fiber mold liquid purge given in 9.
[Claim 11] The manufacture approach of claim 7 to which this fat soluble vitamin is characterized by being vitamin E thru/or a hollow fiber mold liquid purge given in 10.
[Claim 12] The manufacture approach of claim 7 characterized by the average aperture of the barrier layer of this hollow fiber being 0.001-10 micrometers thru/or a hollow fiber mold liquid purge given in 11.

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* NOTICES *

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to a hollow fiber mold liquid purge and its manufacture approach. It is related with the hollow fiber mold liquid purge containing the hollow fiber which consists of a hydrophobic polymer and a hydrophilic polymer especially, the hollow fiber mold liquid purge containing the hollow fiber which consists of a hydrophobic polymer, a hydrophilic polymer, and fat soluble vitamin further, and its manufacture approach.
[0002]
[Description of the Prior Art] Conventionally, in the field of external blood circulation, such as an artificial dialysis machine and a plasma eliminator, the hollow fiber made from a hydrophobic polymer is widely used as a body fluid purge. However, the frequency where the external blood circulation is performed in hemodialysis is high, and the above hollow fiber mold liquid purges will be used over a long period of time, and in the case of external blood circulation, the complication considered to be because for activation of the leucocyte in blood and/or a platelet etc. to arise occurs at the same time, and it has been a dialysis patient's serious problem, for example.
[0003] Moreover, since these body fluid purges contact direct blood and plasma, eluting material test criteria etc. may be established. Therefore, the improvement in the cleanliness of a hollow fiber is an important technical problem.
[0004] In order to form micropore in synthetic macromolecule, the manufacture approach of the hollow fiber which consists of hydrophobic polymers which added hydrophilic polymers, such as a polyvinyl pyrrolidone (PVP) and a polyethylene glycol (PEG), such as polysulfone and a polyamide, is indicated by JP,5-54373,B and JP,2-18695,B.
[0005] Although these hydrophilic polymers are desirable for the improvement in wettability of the film, they are not the objects which exist in a living body originally, and are unnecessary matter for a living body. Therefore, when circulating body fluid, it is desirable to lessen elution of these hydrophilic polymers.
[0006] moreover, among the patients who are performing hemodialysis in the long run, a fall and peroxylipid of the antioxidation operation in blood are a high price -- etc. -- it is checked and the arteriosclerosis nature disease of the long-term dialysis patient considered to originate in this is increasing.
[0007] On the other hand, in order to solve these problems, the artificial organ which covers the coat of the vitamin E which has various physiological functions, such as an antioxidation operation in the living body, a biomembrane stabilization effect, and platelet aggregation depressant action, on the surface of a hollow fiber is proposed. (JP,62-41738,B) However, when the coat of the fat soluble vitamins, such as vitamin E, was carried out to the body fluid purge which consists of a hydrophobic polymer and a hydrophilic polymer as mentioned above, wettability fell, water did not invade into the hole of a hollow fiber, and especially, when it was the hollow fiber mold liquid purge of fine porosity, the usual leak trial was not able to be performed.
[0008]

[Problem(s) to be Solved by the Invention] The place which this invention is made that said technical problem which the conventional technique has should be solved, and is made into the purpose In the manufacture approach of the hollow fiber mold liquid purge containing the hollow fiber which consists of fat soluble vitamins, such as a hydrophobic polymer, a hydrophilic polymer, and vitamin E It is offering the manufacture approach of a hollow fiber mold liquid purge of having reconciled the hydrophilization of a hollow fiber, and maintenance of fat soluble vitamin, and is in originally providing a living body with the hollow fiber mold liquid purge which lessened elution of the hydrophilic macromolecule which is the unnecessary matter.
[0009]
[Means for Solving the Problem] Many above-mentioned purposes are attained by the following hollow fiber mold liquid purge and its manufacture approach of this invention.
[0010] Namely, the hollow fiber which this invention becomes from a hydrophobic polymer and a hydrophilic polymer, the outer case which surround this hollow fiber, and the edge of this hollow fiber -- setting -- between this hollow fiber and these outer cases -- liquid -- with the closure section closed densely This hollow fiber, the body fluid passage containing the hollow fiber lumen ****(ed) by this closure section, the external surface of a hollow fiber, and the 2nd passage formed from this outer case, The body fluid passage inlet port and body fluid passage outlet which are connected with the exterior succeeding the lumen of this hollow fiber, It is the hollow fiber mold liquid purge whose UV (220nm) absorbance of the extract of the hollow fiber by dialysis mold hemodialysis apparatus Manufacturing License Standards it is the body fluid purge which has the 2nd passage inlet port and the 2nd passage outlet which were established in this outer case, and is less than 0.05.
[0011] Moreover, this invention is a hollow fiber mold liquid purge with which this hollow fiber contains fat soluble vitamin.
[0012] Moreover, this invention is a hollow fiber mold liquid purge these whose hydrophobic polymers are polysulfone, polyether sulphone, and a polyamide.
[0013] Moreover, this invention is a hollow fiber mold liquid purge this whose hydrophilic polymer is a polyvinyl pyrrolidone or a polyethylene glycol.
[0014] Moreover, this invention is a hollow fiber mold liquid purge this whose fat soluble vitamin is vitamin E.
[0015] Moreover, this invention is a hollow fiber mold liquid purge whose average aperture of the barrier layer of this hollow fiber is 0.001-10 micrometers.
[0016] Furthermore, the hollow fiber which this invention becomes from a hydrophobic polymer, a hydrophilic polymer, and fat soluble vitamin, the outer case which surround this hollow fiber, and the edge of this hollow fiber -- setting -- between this hollow fiber and these outer cases -- liquid -- with the closure section closed densely This hollow fiber, the body fluid passage containing the hollow fiber lumen ****(ed) by this closure section, the external surface of a hollow fiber, and the 2nd passage formed from this outer case, The body fluid passage inlet port and body fluid passage outlet which are connected with the exterior succeeding the lumen of this hollow fiber, The body fluid purge which has the 2nd passage inlet port and the 2nd passage outlet which were established in this outer case After letting flow the alcoholic water solution of concentration with which this fat soluble vitamin is not eluted, it is the manufacture approach of the hollow fiber mold liquid purge which permutes this alcoholic water solution by the displacing solution which consists of a liquid which does not have harmfulness to water or a living body, and sterilizes this hollow fiber in the condition of having been immersed, subsequently to this displacing solution.
[0017] Moreover, this invention is the manufacture approach of a hollow fiber mold liquid purge that the alcoholic concentration of this alcoholic water solution is 1 - 70%.
[0018] Moreover, this invention is the manufacture approach of a hollow fiber mold liquid purge that these hydrophobic polymers are polysulfone, polyether sulphone, and a polyamide.
[0019] Moreover, this invention is the manufacture approach of a hollow fiber mold liquid purge that this hydrophilic polymer is a polyvinyl pyrrolidone or a polyethylene glycol.
[0020] Moreover, this invention is the manufacture approach of a hollow fiber mold liquid purge

that this fat soluble vitamin is vitamin E.
[0021] Moreover, this invention is the manufacture approach of a hollow fiber mold liquid purge that the average aperture of the barrier layer of this hollow fiber is 0.001-10 micrometers.
[0022]
[Embodiment of the Invention] Drawing 1 is a perspective view showing 1 operation gestalt in case the hollow fiber mold liquid purge of this invention is the hemodialyzer which has a notch in part.
[0023] the both ends as shown in drawing 1 , after the hemodialyzer 10 inserts the hollow fiber bundle 14 which becomes the outer case 13 which has the dialysing fluid passage inlet port 11 and the dialysing fluid passage outlet 12 near both ends from many hollow fibers -- the closure sections 15 and 16 -- the both ends of an outer case 13 -- respectively -- liquid -- it comes to close densely. The headers 19 and 20 which equipped the both ends of an outer case 13 with the body fluid passage inlet port 17 and the body fluid passage outlet 18, respectively were contacted, respectively, and headers 19 and 20 and an outer case 13 have fixed, respectively. When processing body fluid, the tubes 23 and 24 linked to the body etc. are connected with the body fluid passage inlet port 17 and the body fluid passage outlet 18. A polycarbonate, polypropylene, etc. are mentioned as said outer case and a material of a header. Moreover, polyurethane etc. is mentioned as an ingredient of said closure section.
[0024] The above-mentioned hemodialyzer is ****(ed) by two partitions by the hollow fiber and the closure section, and a hollow fiber lumen, the above-mentioned closure section, the body fluid passage formed of the space formed of a header, and the external surface of a hollow fiber and the 2nd passage formed with the above-mentioned outer case are formed. In using the hemodialyzer, blood circulates in the above-mentioned body fluid passage, and dialysing fluid circulates in the 2nd passage of the above.
[0025] Drawing 2 is 1 process drawing of the manufacture approach of a hollow fiber used for the hollow fiber mold liquid purge of this invention.
[0026] Although an example of the manufacture approach of the hollow fiber used for the body fluid purge of this invention is explained below, it is not limited to this.
[0027] It is performed by the spinning equipment containing the spinning undiluted solution tub 2, the core liquid tub 3, the regurgitation nozzle 4, the coagulation solution layer 5, the penetrant remover tub 6, and a winder 7. In addition, various things are known.
[0028] The spinning undiluted solution tub 2 is filled up with the spinning undiluted solution which comes to dissolve a hydrophobic polymer and a hydrophilic polymer in a solvent.
[0029] The case where insufflatio of the air is carried out without using a liquid, the mixed solution of the non-solvent of a hydrophobic polymer, a non-solvent, and a solvent, etc. may be used for the core liquid tub 3. There are water, a methanol, etc. as a non-solvent.
[0030] After adding fat soluble vitamin to a spinning undiluted solution and/or core liquid further or assembling as a body fluid purge in this invention, the coat of the fat soluble vitamin is carried out. In that case, in order to make homogeneity distribute fat soluble vitamin, a surfactant etc. may be added.
[0031] Fat soluble vitamin controls the elution of the water-soluble matter by having various physiological functions, such as an antioxidation operation in the living body, a biomembrane stabilization effect, and platelet aggregation depressant action, and being covered on the surface of a hollow fiber etc.
[0032] The hollow fiber used for this invention consists of a hydrophobic polymer and a hydrophilic polymer. With the combination of these polymers and a spinning undiluted solution presentation, a core liquid presentation, temperature, humidity, etc., a membranous hole configuration can be adjusted and a desired property can be acquired.
[0033] the annular spinning hole (not shown) which is the outer tube of the regurgitation nozzle 4 of double tubing structure about the spinning undiluted solution sent from the spinning undiluted solution tub 2 -- moreover, coincidence is made to breathe out the core liquid sent from the core liquid tub 3 from the inner tube (not shown) of the regurgitation nozzle 4, and it extrudes in air, filling up the core part of a spinning undiluted solution with core liquid. After

carrying out self-weight fall caudad as it is, the freezing characteristic cistern 5 is made to introduce and solidify an extrusion object. As freezing characteristic liquid used for a coagulation cistern, although said non-solvent is used, the solvent of some of said hydrophobic polymer, a surfactant, etc. may also be included.

[0034] The hollow fiber 8 which came out of the freezing characteristic solution layer passes the penetrant remover tub 6, and is rolled round by the winder 7. As a penetrant remover tub, 2 - 5 hours and the 10-90 degrees C of immersion and/or the approaches of carrying out a shower are preferably mentioned to a 20-80-degree C penetrant remover in a hollow fiber 8 for 1 to 8 hours. At the temperature of under said minimum, a detergency is weak about temperature, and the supply equipment and cleaning equipment of a penetrant remover become expensive at the temperature exceeding an upper limit. Said under lower limit of washing is inadequate about this processing time, and when said upper limit is exceeded, working efficiency falls. As a penetrant remover, Milli Q water (RO water) and ultrafiltration water (UF water) are usually used for safety. It cannot be overemphasized that it is not what eliminates that this adds the matter which does not have harmfulness to a living body.

[0035] Moreover, the approach of making a hollow fiber predetermined die length and the bundle of a number, and carrying out high-temperature-hot-water processing in a high pressure vessel as another washing approach, is mentioned. It is 105-130 degrees C preferably, and 100-160 degrees C of hollow fibers 8 are preferably processed for 30 - 120 minutes for 10 to 180 minutes. At the temperature of under said minimum, a detergency is weak about temperature, and problems, like cleaning equipment, such as deformation of a hydrophobic polymer and a high pressure vessel, becomes expensive arise at the temperature exceeding an upper limit. Said under lower limit of washing is inadequate about this processing time, and when said upper limit is exceeded, working efficiency falls. As a penetrant remover, Milli Q water (RO water) and ultrafiltration water (UF water) are usually used for safety. It cannot be overemphasized that it is not what eliminates that this adds the matter which does not have harmfulness to a living body.

[0036] Thus, the hollow fiber obtained is 20-60 micrometers preferably 100-300 micrometers and 5-100 micrometers of thickness the bore of 10-1000 micrometers.

[0037] Moreover, in order to be able to maintain the platelet aggregation depressant action by fat soluble vitamin etc. over a long period of time, as for the content of the fat soluble vitamin in the above-mentioned hollow fiber, it is desirable that it is 1-1000mg/m3, and 10-100mg/m3 is more desirable.

[0038] Moreover, as content in the polymer of the hydrophilic polymer of the above-mentioned hollow fiber (a hydrophobic polymer and hydrophilic polymer), it is 1 - 3% more preferably 0.5 to 4% of the weight.

[0039] After making into a bundle the hollow fiber produced as mentioned above and inserting in an outer case, the hollow fiber membrane bundle end section is closed by closure section agents, such as urethane, a header is attached in both ends, and a hollow fiber mold liquid purge is produced.

[0040] When the average aperture of the detached core of the above-mentioned hollow fiber is 0.001-10 micrometers at this time, the mass transfer for water not invading by ordinary pressure in the detached core hole of a hollow fiber, but purifying body fluid by the above-mentioned washing, is barred. Then, ** it does not carry out elution of the above-mentioned fat soluble vitamin, hydrophilization of the above-mentioned hollow fiber is carried out effectively.

[0041] The assembled body fluid purge performs a leak trial after hydrophilization processing, is filled up with the liquid which does not have harmfulness to water or a living body as a displacing solution, and is sterilized.

[0042] As for the hydrophilization liquid used for hydrophilization processing, it is desirable to carry out in the water solution whose alcoholic concentration is 1 - 70 v/v%, and it is desirable. [further 5 - 50 v/v% of] Hydrophilization of the above-mentioned hollow fiber will not be able to be carried out effectively, but the fat soluble vitamin by which the coat is carried out to the hollow fiber will be eluted less than [this] above this range. A methanol, ethanol, propanol, etc.

are mentioned and the above-mentioned alcohol has desirable ethanol especially.
[0043] Moreover, since the hydrophilic polymer which is not eluted only with water is eluted by processing of this hydrophilization liquid, this hydrophilization processing has the operation to which elution of the hydrophilic polymer is carried out, without making coincidence carry out elution of the fat soluble vitamin to hydrophilization substantially.
[0044] Hydrophilization processing introduces hydrophilization liquid into a body fluid purge, and performs hydrophilization of the whole hollow fiber. Furthermore, water is introduced as a displacing solution and the permutation of hydrophilization liquid and water is performed. By this hydrophilization and water displacement, water can invade into the hole of a hollow fiber, a leak trial can be performed, and mass transfer in a liquid can be further performed through this hole.
[0045] If one of the inlet ports and outlets of body fluid passage or the 2nd passage are opened wide and the water of the passage of another side is substantially discharged after the permutation to a displacing solution is completed, one inlet-port [of the passage of said another side] or outlet side will be closed, and a delivery pressurization condition will be formed for air from another side. In this pressurization condition, after pressurizing a constant pressure, a pressurization side is closed, it acts as the monitor of the pressure of the passage of said another side, and pressure fluctuation is observed. With [a pressure drop] constant value [less than] at this time, the leakage from a hollow fiber or the closure section can be judged to be what is not. If hydrophilization is not fully performed to coincidence, since air leaks, it can also be discovered by this trial from the hole of a hollow fiber with which water has not invaded that hydrophilization is not fully carried out.
[0046] After the above-mentioned leak trial, the liquid which does not have harmfulness to water or a living body as a displacing solution is introduced into body fluid passage and/or the 2nd passage, and a body fluid purge is made full [passage] of these liquids.
[0047] The liquid which does not have harmfulness to a living body means the liquid in which toxicity is not shown, when the liquid inside the body fluid purge after carrying out a priming by the approach which was able to define the body fluid purge of this invention is poured in into the blood vessel of the body.
[0048] It sterilizes by sealing and packing to all the close outlets of a body fluid purge. Said displacing solution may be filled into a package bag without sealing, said body fluid purge may be immersed into it, and you may sterilize by closing a package bag as it is. It is desirable to usually use the small thing of steam permeability for a package bag.
[0049] As sterilization, although autoclave sterilization, gamma ray sterility, etc. are mentioned, if sterilization in the condition of having filled up with the displacing solution is possible, it is good. Autoclave sterilization is more desirable when degradation of safety and an ingredient etc. is taken into consideration.
[0050] The body fluid purge of this invention can decrease the elution volume of PVP to the degree of pole according to sufficient washing and a sufficient hydrophilization process. This can be checked by the elution test of dialysis mold hemodialysis apparatus Manufacturing License Standards. First, after the insufflatio of air etc. removes the liquid with which it fills up from the body fluid purge [finishing / sterilization], a hollow fiber is started and it is made to dry. An extract is performed for 70-degree-C 1 hour using 100ml RO water to 1g of hollow fibers. 220nm UV absorption of an extract is measured.
[0051] The body fluid purge of this invention can attain that the above-mentioned UV absorption is less than 0.05, including a hydrophobic polymer and a hydrophilic polymer. In the desirable case, the above-mentioned UV absorption can attain less than 0.025 further more preferably less than for 0.03.
[0052] As a hydrophobic polymer, polysulfone, polyether sulphone, a polyamide, polyarylate, polymethylmethacrylate, a polycarbonate, a polyether ether ketone, the poly allyl compound ether ketone, cellulose triacetate, cellulose diacetate, etc. are mentioned, and you may use it combining these independence or two sorts or more.
[0053] As a hydrophilic polymer, a polyvinyl pyrrolidone (PVP), a polyethylene glycol (PEG), a polypropylene glycol (PPG), a hide ROKISHI propyl cellulose (HPC), starch, hide ROKISHI ethyl

starch (HES), etc. are mentioned. Especially, PVP and PEG have the well desirable hole plasticity of a hollow fiber.
[0054] As a solvent used for said spinning undiluted solution, dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), dimethylformamide (DMF), etc. are mentioned, and are suitably chosen according to the class of the hydrophobic polymer and the hydrophilic polymer to be used.
[0055] Although vitamin A, beta-carotene, vitamin D, vitamin E, a vitamin K, ubiquinone, etc. are mentioned, in these, vitamin E is suitable for said fat soluble vitamin. Thermal stability of vitamin E is high, it is suitable for industrial production, and the alpha-tocopherol, alpha-tocopherol acetate, alpha-tocopherol nicotinate, the beta-tocopherol, the gamma-tocopherol, delta-tocopherol, etc. are mentioned.
[0056]
[Example] Hereafter, although this invention is explained still more concretely with an example, this invention is not limited to this.
[0057] (Example 1) 15 % of the weight of polysulfones, 9 % of the weight of polyvinyl pyrrolidones, 48 % of the weight of dimethyl sulfoxides, and 28 % of the weight of N,N-dimethylacetamide were mixed, and the spinning undiluted solution was obtained. The bore of 207 micrometers and the hollow fiber of 34 micrometers of thickness were obtained using this spinning undiluted solution and the solution which carries out 0.1 w/v% content of the vitamin E (alpha-tocopherol acetate) as core liquid. 60-degree C RO water shower performed the washing approach for 4 hours. The hemodialyzer of 2 was assembled for the obtained hollow fiber 1.5m of effective film surface products in 9700 bundles.
[0058] The dialysing fluid passage outlet of the hemodialyzer was closed, from the dialysing fluid passage inlet port, ethanol / water =50 / 50 (v/v.%) were introduced by rate-of-flow 500 ml/min, and was circulated for 1 minute, hydrophilization of a hollow fiber was performed, and it permuted by the ethanol water solution which was made to let water flow for 2 minutes and subsequently used RO water in rate-of-flow 500 ml/min from the blood passage inlet port and the dialysing fluid passage inlet port, and was filled up with water in the hemodialyzer.
[0059] The port cap made of silicone resin was inserted in the blood passage inlet port, the blood passage outlet, the dialysing fluid passage inlet port, and the dialysing fluid passage outlet, autoclave sterilization was performed, and the hollow fiber mold hemodialyzer was produced.
[0060] Ethanol/water = (Example 2) Except [all] having performed hydrophilization in 30/70 (v/v.%), it carried out by the same approach as an example 1, and the hollow fiber mold hemodialyzer was produced.
[0061] Ethanol/water = (Example 3) Except [all] having performed hydrophilization in 40/60 (v/v.%), it carried out by the same approach as an example 1, and the hollow fiber mold hemodialyzer was produced.
[0062] (Example 1 of a comparison) Without performing hydrophilization processing by the ethanol water solution, except [all] having been filled up with water in the hemodialyzer, it carried out by the same approach as an example 1, and the hemodialyzer was produced.
[0063] Ethanol/water = (Example 2 of a comparison) Except [all] having performed hydrophilization in 90/10 (v/v.%), a line deed and the hemodialyzer were produced by the same approach as an example 1.
[0064]
[Example(s) of Experiment]
(Leak trial) In order to check the existence of the effectiveness of hydrophilization processing about examples 1, 2, and 3 and the examples 1 and 2 of a comparison, the leak trial which checks leak of the hemodialyzer by pressure variation was performed.
[0065] The leak trial was performed as follows. Insufflatio of the air is carried out to the blood side stream way of the hemodialyzer, and a sealing liquid is discharged. Open a dialysing fluid side stream way inlet port and an outlet wide, close a blood side stream way outlet side, a blood passage inlet port is made to open for free passage with the barostat of 760mmHg(s), it considers as the condition of having pressurized the blood side stream way at 760mmHg(s), and

this condition is maintained for 30 seconds. After closing between a blood side stream way inlet port and barostats and carrying out the closed system of the blood side stream way of the hemodialyzer, the pressure variation for 1 minute in a blood side stream way (**P) is read. When this pressure variation (**P) was below six (mmHg), it was judged that hydrophilization of the whole hollow fiber was carried out. Furthermore on this condition, membraneous ability, such as solute path clearance in a water-solution system, is discovered enough.
[0066] For the result, **P was an example 1 (3mmHg), example 2 (4mmHg) example 3 (4mmHg), the example 1 (207mmHg) of a comparison, and the example 2 (3mmHg) of a comparison.
[0067] (Quantum of a vitamin-E elution volume) About the example 1 and the example 2 of a comparison, in order to estimate the vitamin-E elution volume to the alcoholic water solution used for hydrophilization, it carried out with the extinction method (measurement wavelength of 284nm) by considering the alcoholic water solution which is not processed [of the same presentation as the used alcoholic water solution] as contrast.
[0068] The elution of the vitamin E to the inside of the ethanol / water =50 / 50 (v/v.%) solutions which used the result for hydrophilization in the example 1 was not detected with an extinction method. In the example 2 of a comparison, the total amount of the elution volume of the vitamin E to the inside of the ethanol / water =90 / 10 (v/v %) solutions which were used for hydrophilization was about 1 of amount of vitamin-E immobilization to hollow fiber/5.
[0069] (Eluting material test) In accordance with dialysis mold hemodialysis apparatus Manufacturing License Standards, UV absorption of a hollow fiber was measured about examples 1, 2, and 3 and the examples 1 and 2 of a comparison.
[0070] Results were an example 1 (0.018), an example 2 (0.023), an example 3 (0.019), the example 1 (0.06) of a comparison, and the example 2 (0.015) of a comparison.
[0071]
[Effect of the Invention] The hollow fiber which this invention becomes from a hydrophobic polymer and a hydrophilic polymer, the outer case which surround this hollow fiber, and the edge of this hollow fiber -- setting -- between this hollow fiber and these outer cases -- liquid -- with the closure section closed densely This hollow fiber, the body fluid passage containing the hollow fiber lumen ****(ed) by this closure section, the external surface of a hollow fiber, and the 2nd passage formed from this outer case, The body fluid passage inlet port and body fluid passage outlet which are connected with the exterior succeeding the lumen of this hollow fiber, It is the body fluid purge which has the 2nd passage inlet port and the 2nd passage outlet which were established in this outer case. Since UV (220nm) absorbance of the extract of the hollow fiber by dialysis mold hemodialysis apparatus Manufacturing License Standards is the hollow fiber mold liquid purge which is less than 0.05, there are few effluents from the film at the time of blood contact, and safety is high.
[0072] Moreover, when fat soluble vitamin covers a film front face, this invention can lessen an effluent further, while expecting the bioactive which fat soluble vitamin has, since this hollow fiber contains fat soluble vitamin.
[0073] Moreover, since these hydrophobic polymers are polysulfone, polyether sulphone, and a polyamide, biocompatibility of this invention is high.
[0074] Moreover, since this hydrophilic polymer is a polyvinyl pyrrolidone or a polyethylene glycol, the hole plasticity of this invention of a hollow fiber detached core is good.
[0075] Moreover, since this fat soluble vitamin is vitamin E, it is excellent in thermal stability, and this invention excels [fat soluble vitamin] in industrial productivity.
[0076] Moreover, this invention can carry out hydrophilization of the hollow fiber to the removal and coincidence of a hydrophilic polymer whose average aperture of the detached core of this hollow fiber is 0.001-10 micrometers.
[0077] Furthermore, the hollow fiber which this invention becomes from a hydrophobic polymer, a hydrophilic polymer, and fat soluble vitamin, the outer case which surround this hollow fiber, and the edge of this hollow fiber -- setting -- between this hollow fiber and these outer cases -- liquid -- with the closure section closed densely This hollow fiber, the body fluid passage containing the hollow fiber lumen ****(ed) by this closure section, the external surface of a

hollow fiber, and the 2nd passage formed from this outer case, The body fluid passage inlet port and body fluid passage outlet which are connected with the exterior succeeding the lumen of this hollow fiber, The body fluid purge which has the 2nd passage inlet port and the 2nd passage outlet which were established in this outer case After letting flow the alcoholic water solution of concentration with which this fat soluble vitamin is not eluted, Since it is the manufacture approach of the hollow fiber mold liquid purge which permutes this alcoholic water solution by the displacing solution which consists of water or a liquid harmless to a living body, and sterilizes this hollow fiber in the condition of having been immersed, subsequently to this displacing solution, it excels in biocompatibility and an effluent can be made few to the degree of pole.

[0078] Moreover, since the concentration of this alcoholic water solution is 1 - 70%, this invention does not carry out elution of the fat soluble vitamin substantially, can remove a water-soluble polymer and can carry out hydrophilization of the hollow fiber.

[0079] Moreover, since these hydrophobic polymers are polysulfone, polyether sulphone, and a polyamide, biocompatibility of this invention is high.

[0080] Moreover, since this hydrophilic polymer is a polyvinyl pyrrolidone or a polyethylene glycol, the hole plasticity of this invention of a hollow fiber detached core is good.

[0081] Moreover, since this fat soluble vitamin is vitamin E, it is excellent in thermal stability, and this invention excels [fat soluble vitamin] in industrial productivity.

[0082] Moreover, since the average aperture of the barrier layer of this hollow fiber is 0.001-10 micrometers, this invention can be used for large applications, such as hemodialysis, plasma skimming, and cellular segregation.

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2.**** shows the word which can not be translated.
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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1] It is the perspective view showing 1 operation gestalt of the hollow fiber mold liquid processor of this invention which has a notch in part.
[Drawing 2] It is process drawing showing 1 operation gestalt of the manufacture approach of the hollow fiber used for the hollow fiber mold liquid purge of this invention.
[Description of Notations]
1 Spinning Equipment
2 Spinning Undiluted Solution Tub
3 Core Liquid Tub
4 Regurgitation Nozzle
5 Freezing Characteristic Cistern
6 Penetrant Remover Tub
7 Winder
10 Dialyzer
11 Dialysing Fluid Passage Inlet Port
12 Dialysing Fluid Passage Outlet
13 Outer Case
14 Hollow Fiber Bundle
15 16 Closure section
17 Body Fluid Passage Inlet Port
18 Body Fluid Passage Outlet
19 20 Header
23 24 Connection tube

[Translation done.]

* NOTICES *

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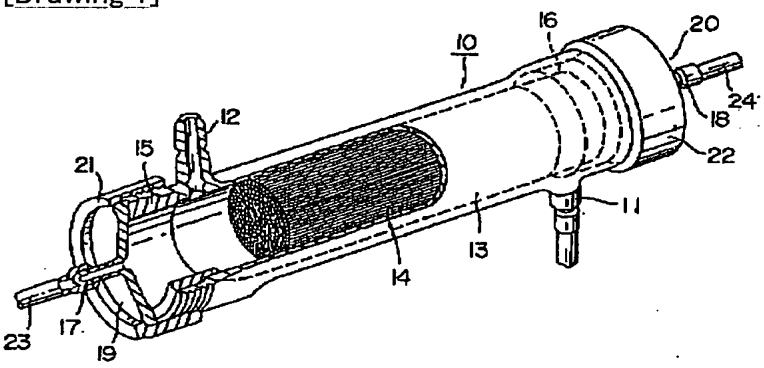
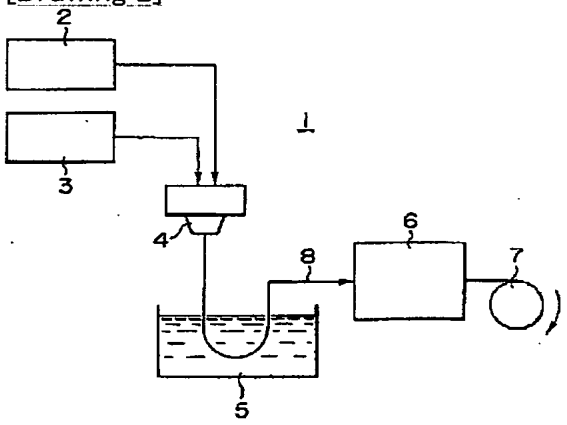
DRAWINGS

[Drawing 1]



[Drawing 2]



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CORRECTION OR AMENDMENT

[Kind of official gazette] Printing of amendment by the convention of 2 of Article 17 of Patent Law
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[Procedure amendment 1]
[Document to be Amended] Specification
[Item(s) to be Amended] Claim
[Method of Amendment] Modification
[Proposed Amendment]
[Claim(s)]
[Claim 1] The hollow fiber which consists of a hydrophobic polymer and a hydrophilic polymer The outer case which surround this hollow fiber the edge of this hollow fiber -- setting -- between this hollow fiber and these outer cases -- liquid -- the closure section closed densely This hollow fiber, the body fluid passage containing the hollow fiber lumen ****(ed) by this closure section, external surface of a hollow fiber, and the 2nd passage formed from this outer case The body fluid passage inlet port and body fluid passage outlet which are connected with the exterior succeeding the lumen of this hollow fiber, and the 2nd passage inlet port and the 2nd passage outlet which were established in this outer case It is the hollow fiber mold liquid purge equipped with the above, and is characterized by UV (220nm) absorbance of the extract of the hollow fiber by dialysis mold hemodialysis apparatus Manufacturing License Standards being less than 0.05.
[Claim 2] The hollow fiber mold liquid purge according to claim 1 characterized by this hollow fiber containing fat soluble vitamin.

[Claim 3] The hollow fiber mold liquid purge according to claim 1 or 2 characterized by this hydrophilic polymer being a polyvinyl pyrrolidone or a polyethylene glycol.
[Claim 4] Claim 1 characterized by the average aperture of the detached core of this hollow fiber being 0.001-10 micrometers thru/or a hollow fiber mold liquid purge given in 3.
[Claim 5] The body fluid passage characterized by providing the following, the external surface of a hollow fiber, and the 2nd passage formed from this outer case, The body fluid passage inlet port and body fluid passage outlet which are connected with the exterior succeeding the lumen of this hollow fiber, The body fluid purge which has the 2nd passage inlet port and the 2nd passage outlet which were established in this outer case The manufacture approach of the hollow fiber mold liquid purge characterized by permuting this alcoholic water solution by the displacing solution which consists of a liquid which does not have harmfulness to water or a living body, and subsequently to this displacing solution sterilizing this hollow fiber in the condition of having been immersed after letting flow the alcoholic water solution of concentration with which this fat soluble vitamin is not eluted The hollow fiber which consists of a hydrophobic polymer, a hydrophilic polymer, and fat soluble vitamin The outer case which surround this hollow fiber the edge of this hollow fiber -- setting -- between this hollow fiber and these outer cases -- liquid -- the closure section closed densely The hollow fiber lumen ****(ed) by this hollow fiber and this closure section
[Claim 6] The manufacture approach of the hollow fiber mold liquid purge according to claim 5 characterized by this hydrophilic polymer being a polyvinyl pyrrolidone or a polyethylene glycol.
[Claim 7] The manufacture approach of a hollow fiber mold liquid purge according to claim 5 or 6 that this fat soluble vitamin is characterized by being vitamin E.

[Translation done.]

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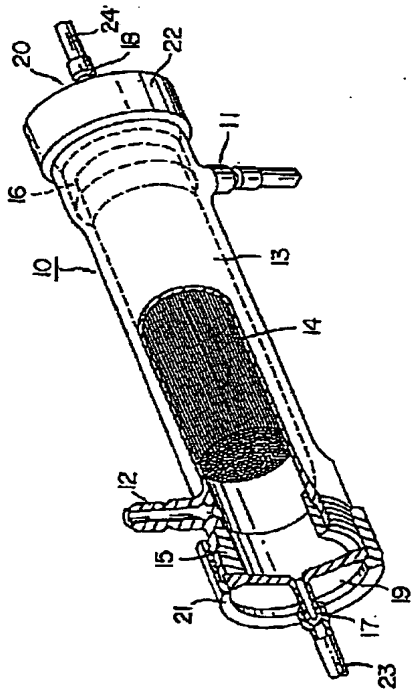
(54)【発明の名称】　中空糸膜型体液浄化装置およびその製造方法

(57)【要約】
【目的】生体適合性に優れ、かつ、溶出物の極度に少ない、疎水性ポリマー、親水性ポリマー、脂溶性ビタミンよりなる中空糸膜型体液浄化装置、およびその製造方法を提供する。
【構成】脂溶性ビタミンを溶出せず、中空糸膜の分離槽の細孔を親水化するアルコール水溶液を用いて親水化し、アルコール水溶液を水に置換後、中空糸膜が水に浸漬された状態で滅菌されてなる。



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【特許請求の範囲】

【請求項１】　疎水性ポリマーおよび親水性ポリマーからなる中空糸膜と、該中空糸膜を取り巻く外筒と、該中空糸膜の端部において該中空糸膜と該外筒との間を液密に封止する封止部と、該中空糸膜と該封止部により隔成される中空糸膜内腔を含む体液流路と中空糸膜の外面と該外筒より形成される第２流路と、該中空糸膜の内腔に連続し外部と接続する体液流路入口および体液流路出口と、該外筒に設けられた第２流路入口および第２流路出口を有する体液浄化装置であって、透析型人工腎臓装置製造承認基準による中空糸膜の抽出液のＵＶ（２２０ｎｍ）吸光度が０．０５未満であることを特徴とする中空糸膜型体液浄化装置。

【請求項２】　該中空糸膜が脂溶性ビタミンを含むことを特徴とする請求項１に記載の中空糸膜型体液浄化装置。

【請求項３】　該疎水性ポリマーが、ポリスルホン、ポリエーテルスルホン、ポリアミドであることを特徴とする請求項１ないし２に記載の中空糸膜型体液浄化装置。

【請求項４】　該親水性ポリマーがポリビニルピロリドンまたはポリエチレングリコールであることを特徴とする請求項１ないし３に記載の中空糸膜型体液浄化装置。

【請求項５】　該脂溶性ビタミンが、ビタミンＥであることを特徴とする請求項２ないし４に記載の中空糸膜型体液浄化装置。

【請求項６】　該中空糸膜の分離層の平均孔径が０．００１～１０μｍであることを特徴とする請求項１ないし５に記載の中空糸膜型体液浄化装置。

【請求項７】　疎水性ポリマー、親水性ポリマーおよび脂溶性ビタミンからなる中空糸膜と、該中空糸膜を取り巻く外筒と、該中空糸膜の端部において該中空糸膜と該外筒との間を液密に封止する封止部と、該中空糸膜と該封止部により隔成される中空糸膜内腔を含む体液流路と中空糸膜の外面と該外筒より形成される第２流路と、該中空糸膜の内腔に連続し外部と接続する体液流路入口および体液流路出口と、該外筒に設けられた第２流路入口および第２流路出口を有する体液浄化装置を、該脂溶性ビタミンが溶出しない濃度のアルコール水溶液を通水した後、該アルコール水溶液を水または生体に為害性のない液体からなる置換液に置換し、次いで該中空糸膜を該置換液に浸漬した状態で滅菌することを特徴とする中空糸膜型体液浄化装置の製造方法。

【請求項８】　該アルコール水溶液のアルコール濃度が１～７０％であることを特徴とする請求項７に記載の中空糸膜型体液浄化装置の製造方法。

【請求項９】　該疎水性ポリマーが、ポリスルホン、ポリエーテルスルホン、ポリアミドであることを特徴とする請求項７ないし８に記載の中空糸膜型体液浄化装置の製造方法。

【請求項１０】　該親水性ポリマーがポリビニルピロリドンまたはポリエチレングリコールであることを特徴とする請求項７ないし９に記載の中空糸膜型体液浄化装置の製造方法。

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【請求項１１】　該脂溶性ビタミンが、ビタミンＥであることを特徴とする請求項７ないし１０に記載の中空糸膜型体液浄化装置の製造方法。

【請求項１２】　該中空糸膜の活性層の平均孔径が０．００１～１０μｍであることを特徴とする請求項７ないし１１に記載の中空糸膜型体液浄化装置の製造方法。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、中空糸膜型体液浄化装置およびその製造方法に関する。特に、疎水性ポリマー、親水性ポリマーからなる中空糸膜を含む中空糸膜型体液浄化装置、さらには疎水性ポリマー、親水性ポリマーおよび脂溶性ビタミンからなる中空糸膜を含む中空糸膜型体液浄化装置ならびにその製造方法に関する。

【０００２】

【従来の技術】従来より、人工透析器、血漿分離器などの体外血液循環の分野においては、体液浄化装置として疎水性ポリマー製中空糸膜が広く利用されている。しかしながら、例えば血液透析においては、その体外血液循環を行う頻度が高く、前述のような中空糸膜型体液浄化装置を長期間に渡って使用することとなり、体外血液循環の際、血液中の白血球および／または血小板の活性化等が生じることによると思われる、合併症等が併発し、透析患者の深刻な問題となっている。

【０００３】また、これらの体液浄化装置は直接血液や血漿と接触するので、溶出物試験基準などが設けられている場合がある。従って、中空糸膜の清浄度の向上は重要な課題である。

【０００４】特公平５－５４３７３号公報、特公平２－１８６９５号公報等には、合成高分子に微細孔を形成するためにポリビニルピロリドン（ＰＶＰ）やポリエチレングリコール（ＰＥＧ）等の親水性ポリマーを添加したポリスルホンやポリアミド等の疎水性ポリマーからなる中空糸膜の製造方法が記載されている。

【０００５】これらの親水性ポリマーは、膜の濡れ性向上のためには好ましいが、元来生体に存在する物ではなく、生体にとっては不要な物質である。従って、体液を流通させた場合、これらの親水性ポリマーの溶出を少なくすることが好ましい。

【０００６】また、長期的に血液透析を行っている患者の中には、血中抗酸化作用の低下や過酸化脂質が高値である等が確認されており、これに起因すると思われる長期透析患者の動脈硬化性疾患が増加している。

【０００７】一方、これらの問題を解決するため、生体内抗酸化作用、生体膜安定化作用、血小板凝集抑制作用などの種々の生理作用を有するビタミンＥの皮膜を中空糸膜の表面に被覆する人工臓器が提案されている。（特

公昭６２－４１７３８号）しかし、上記のようにビタミンＥ等の脂溶性ビタミンを疎水性ポリマーと親水性ポリマーよりなる体液浄化装置にコートした場合、濡れ性が低下し、中空糸膜の孔に水が侵入せず、特に微多孔性の中空糸膜型体液浄化装置の場合、通常のリーク試験を行うことができなかった。

【０００８】

【発明が解決しようとする課題】本発明は、従来技術の有する前記課題を解決すべくなされたものであり、その目的とするところは、疎水性ポリマーと親水性ポリマーおよびビタミンＥ等の脂溶性ビタミンよりなる中空糸膜を含む中空糸膜型体液浄化装置の製造方法において、中空糸膜の親水化と脂溶性ビタミンの保持を両立させた中空糸膜型体液浄化装置の製造方法を提供することであり、また、本来生体に不要な物質である親水性高分子の溶出を少なくした中空糸膜型体液浄化装置を提供することにある。

【０００９】

【課題を解決するための手段】上記の諸目的は、以下の本発明の中空糸膜型体液浄化装置ならびにその製造方法により達成される。

【００１０】すなわち、本発明は、疎水性ポリマーおよび親水性ポリマーからなる中空糸膜と、該中空糸膜を取り巻く外筒と、該中空糸膜の端部において該中空糸膜と該外筒との間を液密に封止する封止部と、該中空糸膜と該封止部により隔成される中空糸膜内腔を含む体液流路と中空糸膜の外面と該外筒より形成される第２流路と、該中空糸膜の内腔に連続し外部と接続する体液流路入口および体液流路出口と、該外筒に設けられた第２流路入口および第２流路出口を有する体液浄化装置であって、透析型人工腎臓装置製造承認基準による中空糸膜の抽出液のＵＶ（２２０ｎｍ）吸光度が０．０５未満である中空糸膜型体液浄化装置である。

【００１１】また、本発明は、該中空糸膜が脂溶性ビタミンを含む中空糸膜型体液浄化装置である。

【００１２】また、本発明は、該疎水性ポリマーが、ポリスルホン、ポリエーテルスルホン、ポリアミドである中空糸膜型体液浄化装置である。

【００１３】また、本発明は、該親水性ポリマーがポリビニルピロリドンまたはポリエチレングリコールである中空糸膜型体液浄化装置である。

【００１４】また、本発明は、該脂溶性ビタミンが、ビタミンＥである中空糸膜型体液浄化装置である。

【００１５】また、本発明は、該中空糸膜の活性層の平均孔径が０．００１～１０μｍである中空糸膜型体液浄化装置である。

【００１６】さらに、本発明は、疎水性ポリマーおよび親水性ポリマーおよび脂溶性ビタミンからなる中空糸膜と、該中空糸膜を取り巻く外筒と、該中空糸膜の端部において該中空糸膜と該外筒との間を液密に封止する封止部と、該中空糸膜と該封止部により隔成される中空糸膜内腔を含む体液流路と中空糸膜の外面と該外筒より形成される第２流路と、該中空糸膜の内腔に連続し外部と接続する体液流路入口および体液流路出口と、該外筒に設けられた第２流路入口および第２流路出口を有する体液浄化装置を、該脂溶性ビタミンが溶出しない濃度のアルコール水溶液を通水した後、該アルコール水溶液を水あるいは生体に為害性のない液体からなる置換液に置換し、次いで該中空糸膜を該置換液に浸漬した状態で滅菌する中空糸膜型体液浄化装置の製造方法である。

【００１７】また、本発明は、該アルコール水溶液のアルコール濃度が１～７０％である中空糸膜型体液浄化装置の製造方法である。

【００１８】また、本発明は、該疎水性ポリマーが、ポリスルホン、ポリエーテルスルホン、ポリアミドである中空糸膜型体液浄化装置の製造方法である。

【００１９】また、本発明は、該親水性ポリマーがポリビニルピロリドンまたはポリエチレングリコールである中空糸膜型体液浄化装置の製造方法である。

【００２０】また、本発明は、該脂溶性ビタミンが、ビタミンＥである中空糸膜型体液浄化装置の製造方法である。

【００２１】また、本発明は、該中空糸膜の活性層の平均孔径が０．００１～１０μｍである中空糸膜型体液浄化装置の製造方法である。

【００２２】

【発明の実施の形態】図１は、本発明の中空糸膜型体液浄化装置が血液透析器である場合の一実施形態を示す一部切欠部を有する斜視図である。

【００２３】図１に示すように、血液透析器１０は、両端部付近に透析液流路入口１１および透析液流路出口１２を有する外筒１３に多数の中空糸膜よりなる中空糸膜束１４を挿入したのち、その両端部を封止部１５、１６で外筒１３の両端部をそれぞれ液密に封止してなるものである。外筒１３の両端には体液流路入口１７および体液流路出口１８をそれぞれ備えたヘッダー１９、２０がそれぞれ当接され、ヘッダー１９、２０と外筒１３とがそれぞれ固着されている。体液を処理する場合、体液流路入口１７および体液流路出口１８には、人体等に接続するチューブ２３、２４が連結される。前記外筒、ヘッダーの素材としては、ポリカーボネート、ポリプロピレン等が挙げられる。また、前記封止部の材料としては、ポリウレタン等が挙げられる。

【００２４】上記血液透析器は、中空糸膜と封止部により２つの区画に隔成され、中空糸膜内腔と上記封止部とヘッダーにより形成される空間により形成される体液流路と、中空糸膜の外面と上記外筒により形成される第２流路とが形成される。血液透析器を使用する場合には、上記体液流路には血液が流通し、上記第２流路には透析液が流通する。

【００２５】図２は、本発明の中空糸膜型体液浄化装置に用いる中空糸膜の製造方法の一工程図である。

【００２６】本発明の体液浄化装置に用いる中空糸膜の製造方法の一例を以下に説明するが、これに限定されるものではない。

【００２７】紡糸原液槽２、芯液槽３、吐出ノズル４、凝固液層５、洗浄液槽６および巻き取り機７を含む紡糸装置により行われる。この他種々のものが知られている。

【００２８】紡糸原液槽２には、疎水性ポリマーと親水性ポリマーを溶媒に溶解してなる紡糸原液が充填されている。

【００２９】芯液槽３には、液体を用いずに空気を吹送する場合や、疎水性ポリマーの非溶媒、非溶媒と溶媒との混合溶液などが用いられる場合がある。非溶媒としては、水、メタノールなどがある。

【００３０】本発明においてはさらに、紡糸原液および／または芯液に脂溶性ビタミンを添加するか、体液浄化装置として組み立ててから、脂溶性ビタミンをコートする。その際、脂溶性ビタミンを均一に分散させるために界面活性剤等を添加してもよい。

【００３１】脂溶性ビタミンは、生体内抗酸化作用、生体膜安定化作用、血小板凝集抑制作用などの種々の生理作用を有し、また、中空糸膜の表面等に被覆されることにより水溶性物質の溶出を抑制する。

【００３２】本発明に用いる中空糸膜は、疎水性ポリマーと親水性ポリマーよりなる。これらのポリマーの組み合わせ、および紡糸原液組成、芯液組成、温度、湿度等により、膜の孔形状を調節することができ、所望の特性を得ることができる。

【００３３】紡糸原液槽２より送液された紡糸原液を２重管構造の吐出ノズル４の外管である環状紡糸孔（図示せず）より、また、芯液槽３より送液された芯液を吐出ノズル４の内管（図示せず）より同時に吐出させ、紡糸原液の芯部に芯液を充填しつつ空気中に押し出す。押出物はそのまま下方に自重落下させた後、凝固性液槽５に導入し凝固させる。凝固液槽に用いる凝固性液としては、前記非溶媒が用いられるが、若干の前記疎水性ポリマーの溶媒、界面活性剤等を含んでもよい。

【００３４】凝固性液層を出た中空糸膜８は、洗浄液槽６を通過させ巻き取り機７により巻き取る。洗浄液槽としては、中空糸膜８を１０～９０℃、好ましくは２０～８０℃の洗浄液に１～８時間、好ましくは２～５時間の間、浸漬および／またはシャワーする方法が挙げられる。温度について前記下限未満の温度では洗浄力が弱く、上限を越える温度では、洗浄液の供給設備や洗浄設備が高価となる。本処理時間について前記下限値未満では洗浄が不十分であり、前記上限値を越えた場合、作業効率が低下する。洗浄液としては、安全性のために通常、逆浸透水（ＲＯ水）や限外濾過水（ＵＦ水）が用いられる。これは、生体に為害性のない物質を添加することを排除するものではないことは言うまでもない。

【００３５】また、もう一つの洗浄方法として、中空糸膜を所定の長さと本数の束にし、高圧容器中にて高温水処理する方法が挙げられる。中空糸膜８を１００～１６０℃、好ましくは１０５～１３０℃で、１０～１８０分、好ましくは３０～１２０分の間処理する。温度について前記下限未満の温度では洗浄力が弱く、上限を越える温度では、疎水性ポリマーの変形、高圧容器等の洗浄設備が高価となるなどの問題が起こる。本処理時間について前記下限値未満では洗浄が不十分であり、前記上限値を越えた場合、作業効率が低下する。洗浄液としては、安全性のために通常、逆浸透水（ＲＯ水）や限外濾過水（ＵＦ水）が用いられる。これは、生体に為害性のない物質を添加することを排除するものではないことは言うまでもない。

【００３６】このようにして得られる中空糸膜は、内径１０～１０００μm、好ましくは１００～３００μm、膜厚５～１００μm、好ましくは２０～６０μmである。

【００３７】また、脂溶性ビタミンによる血小板凝集抑制作用等を長期間にわたって持続しうるためには、上記中空糸膜における脂溶性ビタミンの含有量は１～１０００mg／m^3であることが好ましく、１０～１００mg／m^3がより好ましい。

【００３８】また、上記中空糸膜の親水性ポリマーのポリマー中（疎水性ポリマーと親水性ポリマー）の含有率としては０．５～４重量％、より好ましくは１～３％である。

【００３９】以上のように作製された中空糸膜を束にし、外筒に挿入した後、中空糸膜束端部をウレタン等の封止部剤で封止し、両端部にヘッダーを取り付け、中空糸膜型体液浄化装置を作製する。

【００４０】この時、上記中空糸膜の分離層の平均孔径が、０．００１～１０μmである場合、上記の洗浄により、中空糸膜の分離層孔内には常圧では水が侵入せず、体液を浄化するための物質移動が妨げられる。そこで、上記脂溶性ビタミンを溶出させずに、かつ、効果的に上記中空糸膜を親水化する。

【００４１】組み立てられた体液浄化装置は、親水化処理の後、リーク試験を行い、水あるいは生体に為害性のない液体を置換液として充填して、滅菌される。

【００４２】親水化処理に用いる親水化液は、アルコール濃度が１～７０ｖ／ｖ％の水溶液で行うことが好ましく、さらには５～５０ｖ／ｖ％が好ましい。これ以下では上記の中空糸膜を効果的に親水化することができず、この範囲以上では、中空糸膜にコートされている脂溶性ビタミンが溶出してしまう。上記アルコールは、メタノール、エタノール、プロパノール等が挙げられ、中でもエタノールが好ましい。

【００４３】また、この親水化液の処理により、水のみでは溶出しない親水性ポリマーが溶出するので、この親水化処理は、親水化と同時に脂溶性ビタミンを実質的に溶出させずに親水性ポリマーを溶出させる作用を有するのである。

【００４４】親水化処理は、体液浄化装置に親水化液を導入して、中空糸膜全体の親水化を行う。さらに、置換液として水を導入し親水化液と水との置換を行う。この親水化および水置換により、中空糸膜の孔に水が侵入し、リーク試験を行うことができ、さらには、この孔を通して液体中の物質移動を行うことができるのである。

【００４５】置換液への置換が終了した後、体液流路あるいは第２流路のどちらか一方の入口および出口を開放し、他方の流路の水を実質的に排出したら、前記他方の流路の入口または出口の一方の側を閉鎖し、他方より空気を送り加圧状態を形成する。この加圧状態において、一定圧力に加圧したのち、加圧側を閉鎖し、前記他方の流路の圧力をモニターし、圧力変動を観察する。この時、圧力低下が一定値以内であれば、中空糸膜あるいは封止部等からの漏れはないものと判断できる。同時に、親水化が充分に行われていなければ、水の侵入していない中空糸膜の孔から、空気が漏れるので、この試験により、十分に親水化されていないことも発見することができる。

【００４６】上記リーク試験の後、体液流路および／または第２流路に、置換液として水または生体に為害性のない液体を導入し、これらの液体を体液浄化装置に充満させる。

【００４７】生体に為害性のない液体とは、本発明の体液浄化装置を定められた方法でプライミングした後の体液浄化装置内部の液体を、人体の血管中に注入したときに、毒性を示さない液体をいう。

【００４８】体液浄化装置の全ての入出口に密栓をし、包装して滅菌を行う。密栓をしないで包装袋に前記置換液を満たし、その中に前記体液浄化装置を浸漬し、そのまま包装袋を封止して滅菌を行ってもよい。包装袋には通常水蒸気透過性の小さいものを用いることが好ましい。

【００４９】滅菌としては、オートクレーブ滅菌、γ線滅菌などが挙げられるが、置換液が充填された状態で滅菌可能であればよい。安全性、材料の劣化等を考慮するとオートクレーブ滅菌がより好ましい。

【００５０】本発明の体液浄化装置は、充分な洗浄と親水化工程により、ＰＶＰの溶出量を極度に減少させることができるのである。これは、透析型人工腎臓装置製造承認基準の溶出試験により確認することができる。まず、滅菌済みの体液浄化装置から充填されている液体を空気の吹送等により除去した後、中空糸膜を切り出し、乾燥させる。中空糸膜１ｇに対し１００ｍｌのＲＯ水を用い、７０℃１時間抽出を行う。抽出液の２２０ｎｍのＵＶ吸収を測定する。

【００５１】本発明の体液浄化装置は、疎水性ポリマーと親水性ポリマーを含み、かつ、上記ＵＶ吸収が０．０５未満であることを達成することができる。好ましい場合には、上記ＵＶ吸収が０．０３未満を、さらにより好ましくは０．０２５未満を達成することができるのである。

【００５２】疎水性ポリマーとしては、ポリスルホン、ポリエーテルスルホン、ポリアミド、ポリアリレート、ポリメチルメタクリレート、ポリカーボネート、ポリエーテルエーテルケトン、ポリアリルエーテルケトン、セルローストリアセテート、セルロースジアセテートなどが挙げられ、これらの単独、または２種以上を組み合わせて使用してもよい。

【００５３】親水性ポリマーとしては、ポリビニルピロリドン（ＰＶＰ）、ポリエチレングリコール（ＰＥＧ）、ポリプロピレングリコール（ＰＰＧ）、ハイドロキシプロピルセルロース（ＨＰＣ）、デンプン、ハイドロキシエチルスターチ（ＨＥＳ）等が挙げられる。中でも、ＰＶＰおよびＰＥＧは、中空糸膜の孔形成性が良く好ましい。

【００５４】前記紡糸原液に用いる溶媒としては、ジメチルアセトアミド（ＤＭＡ）、ジメチルスルホキシド（ＤＭＳＯ）、ジメチルホルムアミド（ＤＭＦ）等が挙げられ、用いる疎水性ポリマーおよび親水性ポリマーの種類に合わせて適宜選択される。

【００５５】前記脂溶性ビタミンとは、ビタミンＡ、β－カロチン、ビタミンＤ、ビタミンＥ、ビタミンＫおよびユビキノン等が挙げられるが、これらの中では、ビタミンＥが好適である。ビタミンＥは熱安定性が高く、工業的生産に適しており、α－トコフェロール、α－酢酸トコフェロール、α－ニコチン酸トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール等が挙げられる。

【００５６】

【実施例】以下、本発明を実施例をもってさらに具体的に説明するが、本発明はこれに限定されるものではない。

【００５７】（実施例１）ポリスルホン１５重量％、ポリビニルピロリドン９重量％、ジメチルスルフォキシド４８重量％、N,N-ジメチルアセトアミド２８重量％を混合し、紡糸原液を得た。この紡糸原液と、芯液としてビタミンE（α－酢酸トコフェロール）を０．１ｗ／ｖ％含有する溶液を用いて、内径207μｍ、膜厚34μｍの中空糸膜を得た。洗浄方法は、６０℃のＲＯ水シャワーにて４時間行った。得られた中空糸膜を9700本束ね有効膜面積1.5m^2の血液透析器を組み立てた。

【００５８】血液透析器の透析液流路出口を閉じ、透析液流路入口からエタノール/水=50/50(v/v.%)を、流速５００ｍｌ／ｍｉｎで導入し、１分間流通させ中空糸膜の

親水化を行い、次いでＲＯ水を血液流路入口および透析液流路入口より、流速５００ｍｌ／ｍｉｎにて、２分間通水させ、用いたエタノール水溶液と置換し、血液透析器内に水を充填した。

【００５９】血液流路入口、血液流路出口、透析液流路入口および透析液流路出口にシリコーン樹脂製ポートキャップをはめ、オートクレーブ滅菌を行い中空糸膜型血液透析器を作製した。

【００６０】（実施例２）エタノール/水=30/70(v/v.%)にて親水化を行った以外は、全て実施例１と同様の方法で行い、中空糸膜型血液透析器を作製した。

【００６１】（実施例３）エタノール/水=40/60(v/v.%)にて親水化を行った以外は、全て実施例１と同様の方法で行い、中空糸膜型血液透析器を作製した。

【００６２】（比較例１）エタノール水溶液による親水化処理を行わずに、血液透析器内に水を充填した以外は、全て実施例１と同様の方法で行い、血液透析器を作製した。

【００６３】（比較例２）エタノール/水=90/10(v/v.%)にて親水化を行った以外は、全て実施例１と同様の方法で行行い、血液透析器を作製した。

【００６４】

【実験例】

(リーク試験)実施例１、２、３、比較例１、２について、親水化処理の効果の有無を確認するため、血液透析器のリークを圧力変化によって確認するリーク試験を行った。

【００６５】リーク試験は次のように行った。血液透析器の血液側流路に空気を吹送し、充填液を排出する。透析液側流路入口および出口を開放し、血液側流路出口の側を閉鎖し、血液流路入口を７６０ｍｍＨｇの定圧装置と連通させ、血液側流路を７６０ｍｍＨｇに加圧した状態とし、この状態を30秒間維持する。血液側流路入口と定圧装置との間を閉鎖し、血液透析器の血液側流路を閉鎖系した後、血液側流路内の１分間の圧力変化(△P)を読みとる。この圧力変化(△P)が6(mmHg)以下であれば、中空糸膜全体が親水化されていると判断した。さらにこの条件では、水溶液系での溶質クリアランス等の膜性能が十分発現される。

【００６６】結果は、△Ｐは、実施例１（３ｍｍＨｇ）、実施例２（４ｍｍＨｇ）実施例３（４ｍｍＨｇ）、比較例１（２０７ｍｍＨｇ）、比較例２（３ｍｍＨｇ）であった。

【００６７】(ビタミンE溶出量の定量)実施例１および比較例２について、親水化に用いたアルコール水溶液へのビタミンE溶出量を見積もるため、用いたアルコール水溶液と同じ組成の無処理のアルコール水溶液を対照として吸光度法(測定波長284nm)にて行った。

【００６８】結果は、実施例１では親水化に用いたエタノール/水=50/50(v/v.%)溶液中へのビタミンEの溶出は吸光度法にて検出されなかった。比較例２では、親水化に用いたエタノール/水=90/10(v/v%)溶液中へのビタミンEの溶出量の総量は、中空糸膜へのビタミンE固定化量の約1/5であった。

【００６９】(溶出物試験)実施例１、２、３、比較例１、２について、透析型人工腎臓装置製造承認基準に従い、中空糸膜のＵＶ吸収を測定した。

【００７０】結果は、実施例１（０．０１８）、実施例２（０．０２３）、実施例３（０．０１９）、比較例１（０．０６）、比較例２（０．０１５）であった。

【００７１】

【発明の効果】本発明は、疎水性ポリマーおよび親水性ポリマーからなる中空糸膜と、該中空糸膜を取り巻く外筒と、該中空糸膜の端部において該中空糸膜と該外筒との間を液密に封止する封止部と、該中空糸膜と該封止部により隔成される中空糸膜内腔を含む体液流路と中空糸膜の外面と該外筒より形成される第２流路と、該中空糸膜の内腔に連続し外部と接続する体液流路入口および体液流路出口と、該外筒に設けられた第２流路入口および第２流路出口を有する体液浄化装置であって、透析型人工腎臓装置製造承認基準による中空糸膜の抽出液のＵＶ（２２０ｎｍ）吸光度が０．０５未満である中空糸膜型体液浄化装置であるので、血液接触時に膜からの溶出物が少なく、安全性が高い。

【００７２】また、本発明は、該中空糸膜が脂溶性ビタミンを含むので、脂溶性ビタミンの有する生理活性を期待するとともに、脂溶性ビタミンが膜表面を覆うことにより溶出物を一層少なくすることができる。

【００７３】また、本発明は、該疎水性ポリマーが、ポリスルホン、ポリエーテルスルホン、ポリアミドであるので、生体適合性が高い。

【００７４】また、本発明は、該親水性ポリマーがポリビニルピロリドンまたはポリエチレングリコールであるので、中空糸膜分離層の孔形成性がよい。

【００７５】また、本発明は、該脂溶性ビタミンが、ビタミンＥであるので熱安定性に優れ、工業的な生産性に優れる。

【００７６】また、本発明は、該中空糸膜の分離層の平均孔径が０．００１～１０μｍである親水性ポリマーの除去と同時に中空糸膜を親水化することができる。

【００７７】さらに、本発明は、疎水性ポリマーおよび親水性ポリマーおよび脂溶性ビタミンからなる中空糸膜と、該中空糸膜を取り巻く外筒と、該中空糸膜の端部において該中空糸膜と該外筒との間を液密に封止する封止部と、該中空糸膜と該封止部により隔成される中空糸膜内腔を含む体液流路と中空糸膜の外面と該外筒より形成される第２流路と、該中空糸膜の内腔に連続し外部と接続する体液流路入口および体液流路出口と、該外筒に設けられた第２流路入口および第２流路出口を有する体液浄化装置を、該脂溶性ビタミンが溶出しない濃度のアル

コール水溶液を通水した後、該アルコール水溶液を水あるいは生体に無害な液体からなる置換液に置換し、次いで該中空糸膜を該置換液に浸漬した状態で滅菌する中空糸膜型体液浄化装置の製造方法であるので、生体適合性に優れかつ、溶出物を極度に少なくすることができる。

【００７８】また、本発明は、該アルコール水溶液の濃度が１～７０％であるので、脂溶性ビタミンを実質的に溶出させず、水溶性ポリマーを除去し、中空糸膜を親水化することができる。

【００７９】また、本発明は、該疎水性ポリマーが、ポリスルホン、ポリエーテルスルホン、ポリアミドであるので生体適合性が高い。

【００８０】また、本発明は、該親水性ポリマーがポリビニルピロリドンまたはポリエチレングリコールであるので中空糸膜分離層の孔形成性がよい。

【００８１】また、本発明は、該脂溶性ビタミンが、ビタミンＥであるので熱安定性に優れ、工業的な生産性に優れる。

【００８２】また、本発明は、該中空糸膜の活性層の平均孔径が０．００１～１０μｍであるので、血液透析、血漿分離、細胞分離等広い用途に使用することができる。

【図面の簡単な説明】

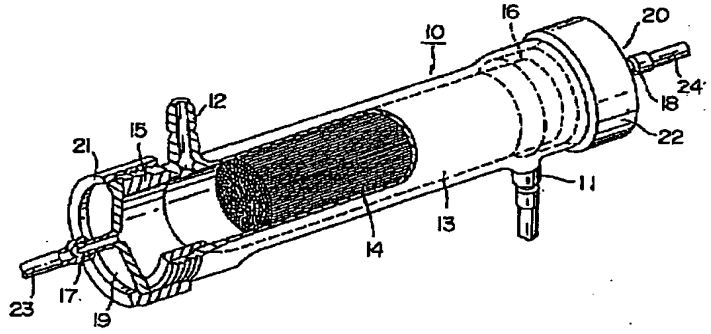
＊【図１】本発明の中空糸膜型体液処理装置の一実施形態を示す一部切欠部を有する斜視図である。

【図２】本発明の中空糸膜型体液浄化装置に用いる中空糸膜の製造方法の一実施形態を示す工程図である。

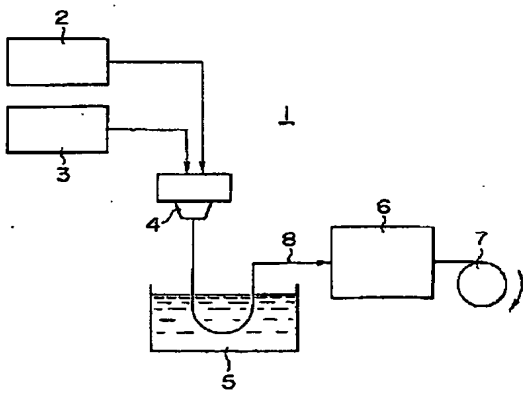
【符号の説明】

1	紡糸装置
2	紡糸原液槽
3	芯液槽
4	吐出ノズル
5	凝固性液槽
6	洗浄液槽
7	巻き取り機
１０	ダイアライザー
１１	透析液流路入口
１２	透析液流路出口
１３	外筒
１４	中空糸膜束
１５、１６	封止部
１７	体液流路入口
１８	体液流路出口
１９、２０	ヘッダー
２３、２４	接続チューブ

【図１】



【図２】



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【手続補正書】
【提出日】平成１２年９月２１日（２０００．９．２１）
【手続補正１】
【補正対象書類名】明細書
【補正対象項目名】特許請求の範囲
【補正方法】変更
【補正内容】
【特許請求の範囲】
【請求項１】　疎水性ポリマーおよび親水性ポリマーからなる中空糸膜と、該中空糸膜を取り巻く外筒と、該中空糸膜の端部において該中空糸膜と該外筒との間を液密に封止する封止部と、該中空糸膜と該封止部により隔成される中空糸膜内腔を含む体液流路と中空糸膜の外面と該外筒より形成される第２流路と、該中空糸膜の内腔に連続し外部と接続する体液流路入口および体液流路出口と、該外筒に設けられた第２流路入口および第２流路出口を有する体液浄化装置であって、透析型人工腎臓装置製造承認基準による中空糸膜の抽出液のＵＶ（２２０ｎｍ）吸光度が０．０５未満であることを特徴とする中空糸膜型体液浄化装置。
【請求項２】　該中空糸膜が脂溶性ビタミンを含むことを特徴とする請求項１に記載の中空糸膜型体液浄化装置。
【請求項３】　該親水性ポリマーがポリビニルピロリドンまたはポリエチレングリコールであることを特徴とする請求項１または２に記載の中空糸膜型体液浄化装置。
【請求項４】　該中空糸膜の分離層の平均孔径が０．００１～１０μｍであることを特徴とする請求項１ないし３に記載の中空糸膜型体液浄化装置。
【請求項５】　疎水性ポリマー、親水性ポリマーおよび脂溶性ビタミンからなる中空糸膜と、該中空糸膜を取り巻く外筒と、該中空糸膜の端部において該中空糸膜と該外筒との間を液密に封止する封止部と、該中空糸膜と該封止部により隔成される中空糸膜内腔を含む体液流路と中空糸膜の外面と該外筒より形成される第２流路と、該中空糸膜の内腔に連続し外部と接続する体液流路入口および体液流路出口と、該外筒に設けられた第２流路入口および第２流路出口を有する体液浄化装置を、該脂溶性ビタミンが溶出しない濃度のアルコール水溶液を通水した後、該アルコール水溶液を水または生体に為害性のない液体からなる置換液に置換し、次いで該中空糸膜を該置換液に浸漬した状態で滅菌することを特徴とする中空糸膜型体液浄化装置の製造方法。
【請求項６】　該親水性ポリマーがポリビニルピロリドンまたはポリエチレングリコールであることを特徴とする請求項５に記載の中空糸膜型体液浄化装置の製造方法。
【請求項７】　該脂溶性ビタミンが、ビタミンＥであることを特徴とする請求項５または６に記載の中空糸膜型体液浄化装置の製造方法。